

METHOD OF TREATMENT

Field Of The Invention

The present invention relates to a method of treating eye and ear infections resulting from parasites and/or infections characterized by the presence of pseudomonas, increased kallikrein and kinin activity. More particularly, there is provided compositions containing a protease inhibitor selected from the group consisting of alpha 1-antitrypsin (AAT), secretory leucocyte protease inhibitor (SLPI) and anti-plasmin inhibitor.

Background Of The Invention

Arachidic acid is liberated in damaged, wounded, or inflamed tissues from phospholipids of cytoplasmatic membranes by the action of phospholipase enzyme and may be then metabolized by the cyclooxygenase cycle (by lipoxygenase enzyme) to prostanoids and eicosanoids. Antiphlogistics of both the steroid and nonsteroid nature, antibiotics, and sulfonamides are often used for therapeutic purposes. The antibiotics which specifically suppress pathogenic microbes and are often used in ophthalmology, are tetracycline, chloramphenicol, bacitracin, and neomycin. Therapeutics which prevent the development of inflammation (antiphlogistics) are both steroid and nonsteroid. The steroid antiphlogistics (e.g., dexamethasone block phospholipase. The anti-inflammatory drugs of nonsteroid nature (e.g., indomethacin, flurbiprofen, piroprofen) block cyclooxygenase and others. The blockage of these enzymes is important, because the products formed in metabolic cycles have a strong chemotactic effect (they cause

accumulation of leukocytes in the sites of origin), (e.g., some leucotrienes) and increase the vascular permeability. This contributes to an excess development of the inflammation. Inflammations, (both of infectious and noninfectious origin) are very dangerous for the anterior and posterior segments of the eye. Thus, scars formed in the cornea during the final stage of the healing process cause the loss of an exceptional function of this tissue, i.e. transparency. The loss of transparency of optical media of the eye (cornea, lens) then leads to a reduction or even loss of sight.

A disadvantage of locally applied antiphlogistics is the relatively low efficiency, retarded healing, and contribution to the development of infection. The local effect of antibiotics is limited.

One of the very prospective possibilities of treatment is the inhibition of plasmin and other destruction proteases (e.g., collagenase or elastase) with specific inhibitors. These enzymes either directly develop the destruction processes (e.g., plasmin) or enable these processes by their own activity (e.g., collagenase, elastase). However, plasmin is effective not only as an initiator developing the degeneration processes proceeding in cascades, but also contributes to an excessive development of inflammation by several other mechanisms of which at least chemotaxis should be mentioned. U.S. Pat. Nos. 5,217,951; 5,290,762, and 5,190,917 which are herein incorporated by reference disclose the treatment of inflammation with serine protease inhibitors alone or in

combination with a corticosteroid. None of the references teach or suggest eye and ear infections caused by parasites or relating to pseudomonas infection.

What is needed then is a medicamentous form for external use as an ophthalmologic or otolaryngologic drug.

This medicamentous form must have strong antiexudative, antiphlogistic, and antimicrobial effect. This medicamentous form is presenting lacking in the prior art.

Summary Of The Invention

The medicamentous form or composition of the present invention is delivered in an aqueous or ointment base particularly suited for ophthalmologic and otolaryngologic application. This medicamentous form contains inhibitors of proteases such as alpha1-antitrypsin, secretory leucocyte protease inhibitor, and anti-plasmin inhibitor trypsin and elastin. These can also be delivered with antiphlogistics and antibiotics.

Accordingly, an object of the present invention is to provide a medicamentous form having strong antiexudative, antiphlogistic and antimicrobial effects.

Still another object of the present invention is to provide a medicamentous form having therapeutic effects including the inhibition of plasmin, leucolytic elastase, and other serine proteases.

Another object of the present invention is to provide a medicamentous form that inhibits the activation of latent forms of some endoproteases and several further subsequent reactions of

chemotaxis and vascularization of the cornea.

Yet another object of the present invention is to treat ear and eye infections characterized by the presence of pseudomonas, excess Kallikerin and Kinin activity.

Detailed Description Of The Preferred Embodiment

The composition of the present invention is a medicamentous form or composition in an aqueous or ointment base particularly suitable for ophthalmologic and otolaryngologic application. The medicamentous form contains inhibitors of proteases such as alpha1-antitrypsin, secretory protease inhibitor and anti-plasmin inhibitor having a concentration of substantially 0.1 to 20 mg. per 1 ml of solution or per 1 g. of ointment base. These inhibitors are applied either individually or in combination after being dissolved in physiological saline or buffer solution with a pH of 6.5 to 7.5, which is advantageously ionically balanced (e.g., phosphate or borax buffer) or present in the ointment base.

The ionically balanced buffer solution means that sodium chloride is added to the buffer solution in such a way that the resulting solution is ionically balanced. For example, the precise performance for borax buffer with pH 7.4 is as follows:

Solution A--1.9 g. $\text{Na}_2\text{P}_4\text{O}_7$ per 100 ml H_2O pro injection.

Solution B--1.25 g. H_3BO_3 + .3 g. NaCl per 100 ml H_2O pro injection. Anti-plasmin inhibitor provides a mix of--10 ml of solution A+90 ml of solution B.

The medicamentous form according to the preferred embodiment in the liquid state may further advantageously contain 0.05 to 15

percent by weight of thickeners selected from the group comprising hydroxypropylmethyl cellulose, methyl cellulose, polyvinylpyrrolidone, polyvinyl alcohol, poly (alkaline glycols), poly/-hydroxyalkyl, (meth)acrylates or poly(meth)acrylamides.

High concentrations of alpha1-antitrypsin or another inhibitor, when locally applied, act not only curably in the advanced stage of disease but also prospectively by the prevention of the formation of destructive processes if timely administered. The vehicles or thickeners with protracted effect then enable a longer contact of the remedy (e.g. AAT) with the tissues.

The medicamentous form according to the preferred embodiment may contain 0.05 to 1.5 percent by weight of steroidal antiphlogistics such as indomethacin or 0.2 to 1 percent by weight of antibiotics such as bacitracin, meomycin, tetracycline, or chloramphenicol and/or hyaluronic acid. Preferred is an antibiotic which is anti-pseudomonas.

The combination of protease inhibitors with antiphlogistics or antibiotics, or all substances together, increases the antiinflammatory and anti-microbial effect because the inhibitors block some products of microbes such as elastase or other proteases. This enables one to use the antibiotics only locally and in smaller doses. The concentration of antiphlogistics may be reduced and, at the same time, the therapeutic effect is higher and the time of treatment shorter which is of great value in healing of tissue.

Ear infections are generally characterized by the presence of

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pseudomonas and increased tissue kallikrein and kinin activity. The more serious the infection, the greater the levels of pseudomoas, kallikrein activity and elastase. The reduction of kallikrein and kinin activity also results in reduction of pain.

Parasitic infestation of the eyes and ears has resulted in increased kallikrein activity and proteases which are released by the parasites. The common parasites which invade the eyes and ears usually through contaminated water generally express serine proteases. The protozoan parasite *Cryptosporidium parvum*, for example, expresses a protease-like component which is recognized by alpha 1-antitrypsin.

Shistosomiasis infections are easily started by *Shistosoma mansoni* entering the eyes and ears of swimmers.

Hyaluronic acid promotes healing and is especially advantageous in treating injury to the cornea.

The medicamentous form is most often applied by instillation or as an ointment into the conjunctival sac. However, it can also be used for irrigation or lubrication of the eye, facial sinuses, and external auditory meatus. It may also be injected into the anterior eye chamber and other places. The medicamentous form in the liquid state may be also present in a hydrophilic three-dimensional polymer matrix in the form of a strip, contact lens, and the like from which the active components are released. The incorporation of medicamentous form into a hydrophilic matrix can be performed according to the invention by conditioning of the matrix in the solution of medicamentous form in order to obtain the

required concentration of inhibitors and also for the antiphlogistics and antibiotics in polymer matrix.

The invention is illustrated in the examples of performance and the examples are provided without the intention of limiting the scope of the present invention.

The preparation of medicamentous form in liquid state is begun by separately dissolving each substance in a small amount (10 to 40 ml) of buffer or physiological saline.

The ointment base is prepared by melting 10 g. lanolin, 10 g. liquid paraffin, and 80 g. white vaseline in bath water. The mixture is then strained through a hydrophilic gauze and sterilized. If the applicable therapeutic is easily soluble in water, it is dissolved in the necessary amount of distilled water for the preparation of injections, mixed with the ointment base in part melted in a water bath and stirred until completely cooled. If the therapeutic is insoluble in water, it is used for the preparation in the finest powdered form. However, it is first titrated in a smaller amount of liquid paraffin and then mixed with the ointment base.

Example 1

A mixture is provided by combining alpha 1-antitrypsin hydroxypropyl methyl cellulose 1 g.; and ionically balanced borax buffer of pH 7.4 up to 100 g. Drops of this composition dosed into the conjunctival sac of a patient at intervals of 3 hours heals allergic conjunctivitis within 3 to 5 days.

Example 2

A mixture is provided by combining alpha 1-antitrypsin 0.005 g.; hydroxypropyl methyl cellulose 2.5 g.; and ionically balanced phosphate buffer of pH 7.4 up to 100 g. The drops were dosed into the ear of a patient with swimmer's ear three times a day. Pain was reduced with the initial dose.

Example 3

A mixture is prepared by combining alpha 1-antitrypsin 0.005 g.; polyvinylalcohol a g.; 0.001g of hyaluronic acid and ionically balanced borax buffer of pH 7.4 up to 100 g. Drops of the mixture were applied into the conjunctival sac of the patient at intervals of 2 hours. This heals minute wounds of the conjunctive, cornea, and eyelids within 2 to 4 days.

Example 4

A mixture is prepared by combining 0.2 g.; hydroxypropyl methyl cellulose 2.5 g.; and physiological saline up to 100 g. An etched and burnt cornea can be healed during 4 days by application of the drops four times a day. The transparency of the cornea can be recovered either completely or at least in the periphery of the cornea.

Example 5

A mixture is prepared combining SLPI 0.01 g.; dexamethasone sodium phosphate 0.1 g.; hydroxypropyl methyl cellulose 2.5 g.; and ionically balanced borax buffer up to 100 g. The eye drops can be used to heal severe allergic conjunctivitis by instillation three times a day.

Example 6

A mixture is prepared by combining alpha 1-antitrypsin 0.1 g.; dexamethasone sodium phosphate 0.5 g.; hydroxypropyl methyl cellulose 2 g.; 0.58 hyaluronic acid and ionically balanced phosphate buffer up to 100 g. The drops can be administered into an infected ear 3 times a day. Pain and inflammation will be reduced immediately.

Example 7

A mixture is prepared by combining 0.1g. of alpha 1-antitrypsin 0.05 g. of hyduronic acid 0.05 g.; dexamethasone sodium phosphate 0.1 g.; chloramphenicol 0.5 g. and physiological saline up to 100 g. The solution can be used in the treatment of rhinal allergoses and allergoses of meatus acusticus externus.

Example 8

Ten patients from India suffering from parasitic infestation of the eyes resulting from exposure in the Ganges river and exhibiting red inflamed eyes were treated with a 5% solution of alpha 1-antitrypsin in saline solution. Immediately after the application of three drops to each of the eyes of the patients, the redness of the inflammation disappeared.